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Is there cardiac risk in Generalized Anxiety Disorder? Does this relationship shed light on future treatment protocols?

Ventricular repolarization parameters in Generalized Anxiety Disorder

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Abstract
Aim: Generalized anxiety disorder (GAD) is a subtype of anxiety disorder that differs in symptoms and clinical findings. There is excessive and pervasive worry about everyday life conditions, physical performance in GAD. Changes in ventricular repolarization may play a role and interact with this process. Therefore, this study aimed to investigate whether ventricular repolarization parameters interact with the level of GAD and highlight for followed-up treatment.
Material and Methods: One hundred eighteen patients (non-smoker, non-alcoholic) without a previous psychiatric disease who were newly diagnosed with GAD were included in this study between March 2021 and February 2022. One hundred twenty healthy individuals who did not have any psychiatric or organic disorder and whose Hamilton Anxiety Rating Scale (HAM-A) score was below five were taken as the control group. A 12-lead ECG was taken at enrolment. The ventricular repolarization parameters were calculated.
Results: The individuals participating in the study were divided into two groups: GAD and control groups. There was no statistically significant difference between the two groups regarding demographic characteristics. The TG level (p=0.049) was higher than in the GAD group. Six parameters, including age, gender, TG, Tpeak-Tend interval (Tp-e), QT dispersion, and heart rate were entered into logistic regression analysis. QT dispersion (OR: 1.122; 95%CI:1.081-1.165;p<0.001) and heart rate (OR: 1.039; 95%CI:1.002-1.076 ;p<0.037) were found to be independent predictors of GAD.
Discussion: QT dispersion associated with ventricular arrhythmia is a simple test that should be closely monitored in patients with GAD and is an important criterion for establishing treatment protocol including drug and physical exercise.

Keywords
QT, Interval, Anxiety Disorder, Electrocardiogram

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Introduction

Generalized anxiety disorder (GAD), seen in 5% of the population, is a psychiatric condition characterized by chronic disquiet and worry that is difficult to control [1]. Environmental, biological, and neuropsychological factors play a role in GAD etiopathogenesis [2]. The effects of the autonomic nervous system (ANS) regulating heart rhythm are generally observed in GAD. Sympatho-vagal imbalance triggers stress, which has a negative effect on physical performance and causes GAD. The characteristic symptoms of GAD, such as palpitations, sweating, and tremors, are seen in ANS dysfunction [3]. In addition, ANS dysfunction may cause ventricular repolarization changes and predispose to cardiac arrhythmias [4].

Electrocardiogram (ECG) is one of the most common tests used to diagnose cardiovascular diseases. Measurements of the QT interval and QT dispersion (QTd) in ECG are related to the ventricular repolarization process and are predictors of ventricular arrhythmias. Therefore, prolonged QT interval and QTd can cause sudden cardiac death [5]. T-wave measurements have been recently used to evaluate ventricular repolarization. In studies, T-wave parameters and the ratio of these parameters to QT interval were reported as new indicators for ventricular repolarization. The Tpeak-Tend interval (Tp-e) and QTd, reflecting the transmural dispersion of repolarization are calculated through ECG [6]. Evaluation of these ECG parameters in GAD is considerable for the future prevention and follow-up of primary disease

Material and Methods

Study Design

In this case-control study, 138 consecutive patients (no psychiatric history, no drug use, no smoking or alcohol use) who applied to the psychiatry outpatient clinic and were diagnosed with GAD for the first time according to the GAD criteria of DSM-5 were included between March 2021 and February 2022. Twenty patients with a history of hypertension, left bundle branch block pattern on ECG, anemia, moderate to severe heart valve disease, evidence of active infection, and coronary artery disease were excluded from the study. The remaining 118 patients were included in the study as the GAD group. One hundred-twenty patients were taken as the control group. Hamilton Anxiety Rating Scale (HAM-A) was administered to all participants. The control group consisted of healthy individuals with a HAM-A score below five and without a psychiatric history. In order to conduct this study, the required permission and consent were obtained from the Clinical Research Ethics Committee of the Faculty of Medicine, Kahramanmaras Sutcu Imam University (30.04.2019- decision No: 06).

Definition of Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) was diagnosed according to DSM-5 anxiety GAD criteria. HAM-A test scale was applied to each participant between 13:00 and 14:00 of the day. An environment where the participants felt comfortable was provided. The total score was obtained according to the appropriate answer to 14 questions on the scale.

Electrocardiographic and Echocardiographic Parameters

All participants underwent a 12-lead ECG using Nihon Kohden's (Tokyo, Japan) ECG device at 50 mm/s speed and 10 mm/mV amplitude at rest. ECGs were evaluated by two specialist physicians using a magnifying glass to obtain an accurate measurement. The QT interval was measured to the time from the start of the QRS complex to the end of the T wave. The QT interval was calculated by averaging leads V4 and V5 if lead V5 was insufficient for the measurement. The QT intervals in the 12 leads were recorded separately to calculate the QTd. The QTd was calculated by subtracting the longest and shortest QT times. The Tp-e interval was measured to the time from the peak of the T wave to the end of the T wave. The end of the T wave was defined as the intersection of the line tangent to the downslope of the T wave with the isoelectric line. Heart rate-corrected QT (cQT) and Tp-e (cTp-e) intervals, Tp-e/QT and Tp-e/cQT ratios were calculated using Bazett's formula.

Images of all participants were obtained from the parasternal and apical window in the lateral decubitus position using the Philips EPIQ 7C (Philips Healthcare, MA, USA) echocardiography device. Left ventricular ejection fraction was calculated using Simpson's method.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows 21 program was used for statistical analysis. Categorical variables were expressed as percentages and continuous variables as mean ± standard deviation. The participants were divided into two groups as GAD and the control group. The Kolmogorov-Smirnov test, skewness, and kurtosis were used for the assessment of normal distribution. The independent t-test was used for continuous variables with normal distribution. The Chi-square test was performed on categorical variables. Binary logistic regression analysis was applied to evaluate the effects of age, gender, triglyceride (TG), Tp-e interval, QTd, and heart rate parameters on GAD. Interobserver agreement of the data was calculated using the Bland-Altman analysis, and intraclass correlation coefficients were used to assess intraobserver agreement. A 2-sided p-value of <0.05 was considered statistically significant.

Results

All participants were separated into two groups: GAD and the healthy control group. Forty-six of the GAD group were male, with the mean age of 36,88 years. The control group consisted of 50 men, with the mean age of 41,7 years. There was no statistically significant difference between the two groups regarding biochemical parameters and demographic characteristics, except for TG ($p=0.049$) (Table 1). The comparison of the two groups in terms of electrocardiographic findings is shown in Table 2. In addition, box-plot graphs of ECG parameters showing a statistically significant difference between the two groups are shown in Figure 1. A correlation analysis evaluated the relationship between HAM-A score and ECG parameters applied to all participants. Among the parameters shown in Table 3, the Tp-e/QTc ratio parameter was not significantly correlated between the two groups.

Age, gender, TG, Tp-e, QTd, and heart rate were entered into the logistic regression analysis, QTd (OR: 1.122; 95%CI:1.081-1.165;$p<0.001$) and heart rate (OR: 1.039; 95%CI:1.002-1.076 ;$p<0.037$) were found to be independent predictors of GAD (Table 3).

Table 1. Demographic and laboratory parameters of the participants

	GAD group (n=118)	Control group (n=120)	p
Age	36.88±4.26	35.83±5.37	0.097
Male, n%	39	41.7	0.673
BMI	26.39±3.16	27.10±3.34	0.092
Creatinine, mg/dl	0.77±0.20	0.79±0.20	0.562
Glucose, mg/dl	101.74±9.95	100.86±9.12	0.478
Total cholesterol. mg/dl	197.11±35.59	193.90±29.88	0.435
HDL, mg/dl	50.09±7.05	50.02±7.43	0.939
LDL, mg/dl	117.11±24.29	111.01±24.80	0.056
TG, mg/dl	182.79±71.49	166.46±54.99	0.049
Sodium, mEq/L	141.16±2.53	140.56±3.17	0.112
Potassium, mEq/L	4.27±0.30	4.29±0.44	0.806
Calcium, mg/dl	8.90±0.37	8.83±0.48	0.183
Magnesium, mg/dl	1.85±0.14	1.86±0.14	0.825

Abbreviations: BMI; body mass index, GFR; Glomerular Filtration Rate, HDL; High-Density Lipoprotein, LDL; Low-density lipoprotein, TG; Triglyceride

Table 2. Electrocardiographic and echocardiographic parameters of the participants

	GAD group (n=118)	Control group (n=120)	p
LVEF. %	64.88±3.79	64.98±3.84	0.848
IVST, mm	11.16±0.98	10.75±0.94	0.159
PWT, mm	8.03±1.22	7.86±1.02	0.255
Heart rate, bpm	81.89±7.56	80.06±9.18	0.095
QT interval, ms	362.16±11.27	358.66±9.08	0.009
Maximum QT interval, ms	385.76±9.36	379.81±8.05	<0.001
Minimum QT interval, ms	352.64±9.38	353.91±7.62	0.253
QTd, ms	33.11±8.07	25.90±8.07	<0.001
cQT interval, ms	422.72±24.33	413.82±28.56	0.010
Tp-e interval, ms	72.20±8.26	68.68±9.39	0.034
cTp-e interval, ms	84.26±10.35	79.33±12.65	0.014
Tp-e/QT ratio	0.19±0.02	0.19±0.02	0.139
Tp-e/cQT ratio	0.17±0.02	0.16±0.02	0.502

Abbreviations: LVEF; left ventricular ejection fraction, IVST; interventricular septal thickness, PWT; posterior wall thickness, QTd; QT dispersion

Table 3. Correlations between HAM-A score and electrocardiographic parameters / Independent predictors of generalized anxiety disorder

	r	p
QT interval	0.151	0.019
QTc interval	0.189	0.004
QT dispersion	0.287	0.001
Tp-e interval	0.181	0.005
cTp-e interval	0.218	0.001
Tp-e/QT ratio	0.144	0.027
Tp-e/cQT ratio	0.068	0.297

	B	OR	p	95% CI	
				Lower	Upper
Age	0.049	1.050	0.101	0.990	1.114
Male	0.083	1.086	0.792	0.587	2.011
IVST	0.004	1.004	0.086	0.999	1.009
Tp-e	0.028	1.029	0.118	0.993	1.065
QT dispersion	0.115	1.122	<0.001	1.081	1.165
Heart rate	0.038	1.039	0.037	1.002	1.076

Abbreviations: IVST; interventricular septal thickness

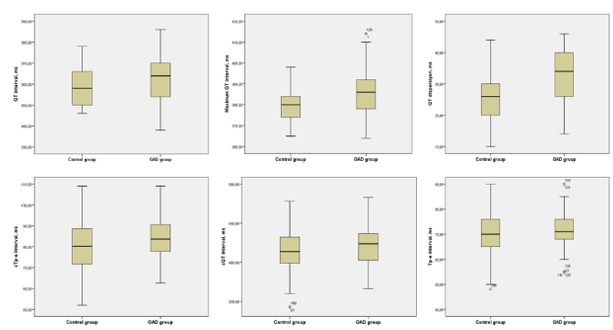

Figure 1. The box plots showing the electrocardiographic parameters according to the GAD and control group

Discussion

GAD, a branch of anxiety, is a common disease in society. In addition, GAD is associated with many cardiovascular disorders [7]. Ventricular arrhythmia is one of these cardiovascular disorders. Prolonged Qt and Tp-e intervals in ECG cause ventricular arrhythmias by affecting ventricular repolarization [8]. This is the first study we know to compare the QTd, Tp-e and Tp-e/QT parameters, which are new ECG parameters associated with ventricular repolarization, in GAD patients (without any history of psychotropic drugs, smoking, or alcohol). Anxiety is the cause and consequence of many diseases. Anxiety can affect cardiac functions and lead to conditions that can progress to sudden cardiac death [9]. The mechanism of how it causes sudden cardiac death is not fully explained. However, it has been suggested that this situation can be expressed by ANS dysfunction. Studies show that decreased parasympathetic activity and increased sympathetic activity may predispose to malignant arrhythmias and cause sudden cardiac death [10]. In hypertensive patients with anxiety, cardiac heart rate variability indices, which are indicators of cardiac autonomic imbalance, were found to be correlated with the severity of anxiety [11]. The effect of psychiatric drugs used in the treatment can change the QT interval in the ECG and should be followed closely to prevent arrhythmia complications. QTd, obtained from the difference between maximum QT and minimum QT in the 12-lead ECG, reflects ventricular repolarization instability. This electrical imbalance in ECG leads has been shown to increase susceptibility to malignant ventricular arrhythmias and is associated with sudden cardiac death [12]. We showed that QT and cQT interval durations were found to be higher in the GAD group, and QTd was an independent predictor of GAD. This may be because the max interval times were higher in the GAD group. There are also studies showing that it is not directly involved in ventricular repolarization. Increased QTd in GAD in our study may be a marker of instability of autonomic functions of the heart.

Tp-e interval is one of the parameters that evaluate ventricular repolarization in the ECG. The Tp-e interval has been shown to be superior to QTd in demonstrating ventricular heterogeneity. Tp-e/QT and Tp-e/cQT ratios are not affected by heart rate,

Tp-e and QT intervals change with heart rate [13]. Tp-e and Tp-e/QT parameters were found to be predictors of ventricular arrhythmia in studies conducted with schizophrenia and parkinsonian patients with ANS dysfunction [14]. Tp-e interval has also been associated with mortality in Brugada syndrome, ST-elevation myocardial infarction, and congenital QT syndromes. Increased Tp-e may cause malignant ventricular arrhythmias; therefore, it may affect mortality [15]. In our study, while the Tp-e/QT ratio was not different between the two groups and showed a weak correlation with HAM-A score, Tp-e alone was significantly higher in patients with GAD. We can say that both the QT interval and Tp-e interval are higher in the GAD group compared to the healthy control group. The ratio of the two parameters to each other did not make a significant difference in both groups.

Studies prove that GAD is associated with many cardiac and non-cardiac diseases [16]. A relationship was found between high cholesterol and TG levels in GAD patients without coronary heart disease [17]. The TG elevation was found to be higher in the GAD group, similar to this study. In addition, it has been shown that GAD is also correlated with obesity [18]. The BMI values were found to be similar between both groups in our study. Age is an essential factor in GAD. There was an increase in the frequency of GAD and HAM-A score over 65 years of age. This situation has been attributed to organic pathologies that increase with age. In our study, since organic diseases were excluded, the mean age was low and included relatively young adults.

Sadip et al reported the effect of cardiopulmonary exercise on modulating stress, ventricular depolarization and repolarization. They said that stress negatively affects physical performance and cardiac rhythm such as ventricular repolarization. They evaluated stress levels with DASS (depression anxiety stress scale), ECG used for evaluating QTc interval and T peak to T end interval. They found that blowing balloon exercise (part of breathing exercise) improves ECG parameters and decreases the level of stress. They correlated with the level of stress and cardiac arrhythmia. Therefore, they aimed to activate the parasympatho-vagal with physical exercises, which provide active cardiac vagal fiber's activity connected with the vagal nerve. Also, they determined that when the lung volume increases, SARs (adapting pulmonary stretch receptors) can activate and stimulate the cardiac vagal nerve [19]. This study showed that the Tp-e/QT ratio was not different between the two groups and showed a weak correlation with HAM-A score, Tp-e alone was significantly higher in patients with GAD. We can say that both the QT interval and Tp-e interval are higher in the GAD group compared to the healthy control group. We investigated the connection between anxiety and cardiac arrhythmia parameters for establishing prediction factors for GAD. However, we did not use the treatment protocol for decreasing stress factors and encouraging cardiac parameters, but we will establish the current comprehensive treatment protocol with the next research.

Our study has some limitations. It was conducted with a relatively small number of patients, the type of arrhythmia and the frequency of arrhythmia were not evaluated with 24-hour-Holter ECG recordings. In addition, the patients with GAD were not followed up for many years as a prospective cohort study.

Conclusion

The QTd was an independent predictor of GAD in the comparison of ECG parameters evaluating ventricular repolarization in GAD patients. Patients with GAD should be followed closely regarding ventricular arrhythmia, paying attention to the increase in the QT interval both in drug use and in the follow-up of physical exercises.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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